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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,839	03/23/2001	Michael S.C. Fung	TNX00-04	6910

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TANOX, INC.
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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,839	FUNG ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,20,22-30 and 32-35* is/are pending in the application.

4a) Of the above claim(s) *28-30 and 32-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,20 and 22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

This application claims priority to provisional application 60/191,429.

Claims 1-18, 21 and 31 have been canceled.

Claims 19, 20, 22-30 and 32-35 are currently pending.

Claims 28-30 and 32-35 stand withdrawn as being drawn to a non-elected invention.

Claims 19, 20 and 22-27 are the subject of examination in the present Office Action.

1. The following ground of rejection has been maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 20 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim is not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation of an antibody which inhibits "complement activation at a molar ratio of about 1:2 (antibody to C2) ". There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes new matter.

Applicant's arguments filed October 20, 2003 have been fully considered but they are not persuasive. Applicant contends that the recitation of "about" has been removed from the claims. While the recitation was deleted from claim 19, it remains in claim 20. accordingly, the ground of rejection is maintained for the reasons of record.

3. Upon review, the following ground of rejection has been reinstated. As the reinstatement was not necessitated by Applicant's amendment, this action is made NON-FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 19, 20, 23 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661)(IDS; of record).

Anderson et al teaches a monoclonal antibody produced by a hybridoma cell line, which binds to C2a or to the C2a portion of C2 that inhibits the classical pathway (page 660; paragraph bridging columns in particular) and a pharmaceutical composition comprising same with an acceptable carrier (in phosphate-buffered saline; Fig. 1 in particular)[claim 27]. Applicant has amended claims 19 and 20 to recite the limitation that the antibody "inhibits" complement activation "at a molar ratio of 1:2 (antibody to C2)." Applicant asserts in the reply filed March 13, 2003 that the antibody taught by Anderson "requires a 7 fold molar excess of antibody to C2 in order to achieve a 50% inhibition of C2 hemolytic activity" and that "[f]igure 3 illustrates that the present invention antibodies are capable of inhibiting the classical pathway at a molar ratio of 1:2," concluding, "[t]herefore, the present claims are not anticipated by the Anderson reference." It is acknowledged that the degree of complement inhibition by the Anderson antibody may not be as high as the inhibition by 175-62 of the present invention, the only antibody for which "molar" data is given. However, the claims are drawn to "inhibition" at the 1:2 ratio, not ablation. It is respectfully submitted that the threshold for "inhibition" is low, the accepted meaning of the word in biological terms as a decrease, limit, or block of the action or function of a target. Accordingly, in order to satisfy the metes and bounds of the claims, the Anderson antibody only has to decrease complement activation when incubated with C2 at a ratio of 1:2. The term does not require a complete ablation of complement activation. Accordingly, while Anderson does not specifically state that the antibody can cause a decrease in complement activation when at a antibody:C2 ratio of 1:2, silence about a particular property does not necessarily constitute the absence of said property. There is equally no showing that the antibody of Anderson does not inhibit at the recited ratio and no side-by-side

comparison to show that the instantly disclosed antibodies possess properties not found in the prior art antibody. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the materials, i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is on the Applicant to prove that the claimed materials are different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

5. The following represent new grounds of rejection in this NON-FINAL Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 27 is drawn to a "pharmaceutical composition" comprising an antibody that binds to C2a and inhibits complement activation at a ratio of 1:2 (antibody to C2). The recognized utility for a pharmaceutical composition is for the treatment of a condition *in vivo* or *ex vivo*. However, the specification is not enabling for the treatment of any condition. The specification discloses that antibodies of the present invention are capable of binding C2a, capable of inhibiting complement activation via the classical pathway and infers that the antibodies are capable of inhibiting the lectin pathway due the requirement for C2a in said pathway. The specification also teaches that the antibodies of the present invention have no effect on the alternative complement activation pathway (Figure 4 for example). The specification also provides a listing of conditions in which down-regulation of complement activation is effective for treatment (page 5, line 11 to page 6, line 8 for example). However, the specification does not teach any actual treatment using the antibodies of the invention, rather the specification merely discloses potential routes of information (page 13, lines 5-11 for example),

"estimated dosage of such antibodies" (page 13, lines 12-15 for example) and that "therapeutic activity of C2a inhibitor molecules in various inflammatory and autoimmune manifestations" can be elucidated via further experimentation (page 16, lines 1-16 for example). Accordingly, the specification fails to provide sufficient guidance regarding dosage or application of the antibodies of the present invention and the artisan would therefore not be able to predict that any of the antibodies disclosed would be effective in the treatment of any condition. Further, the fact that the antibodies are not effective against the alternative pathway allows for the possibility that any condition in which the present antibodies were effective in inhibiting the classical or lectin pathway of complement activation would be able to escape regulation via the alternative pathway.

Accordingly, the specification does not adequately teach how to use the claimed "pharmaceutical" composition. In view of the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is indefinite and ambiguous to recite the laboratory name "175-62" in claims 25 and 26 to identify the antibody. The same designation may likely to be used by others as well to designate different cell lines. It is suggested that the corresponding accession or deposit number from an acceptable depository be recited in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661; of record) in view of Janeway et al, Immunolobiology, 3rd edition, Current Biology Ltd, London, England 1997 pages 13:7-8; of record), Vakeva et al. (Circulation. [1998] 97(22):2259-2267; U on form PTO-892, newly cited) and Stoltzner et al (Am J Pathol. [2000]156(2):489-499; V on form PTO-892, newly cited).

Anderson has been discussed supra.

Anderson does not teach a humanized form of the antibody as recited in claim 7.

Janeway teaches standard techniques in the art at the time the invention was made including that humanized antibodies comprise the CDRs of a mouse monoclonal antibody onto the human framework of a human immunoglobulin, and that said chimeric antibodies are far less immunogenic in humans than the parent mouse monoclonal antibodies, and thus they can be used for treatment of humans with far less risk of anaphylaxis than the parent non-human monoclonal antibodies. For similar purposes, monoclonal antibodies that are entirely human in origin can be made in mice lacking endogenous immunoglobulin genes.

Vakeva teaches that "[s]everal lines of investigation support a role for complement in the pathogenesis of [myocardial infarction/reperfusion] injury" (page 2259, first column in particular). Vakeva teaches that treatment of rats with an anti-C5 antibody "significantly inhibits cell apoptosis, necrosis and [peripheral mononuclear cell] infiltration in the rat despite C3 deposition" (Abstract in particular). C5 is known in the art to be a "late" component in the complement cascade and C3 is similarly known to be an "early" or "middle" component.

Stoltzner teaches that the complement system mediates the inflammatory response activated in Alzheimer's disease (AD; Abstract in particular). Stoltzner teaches that AD amyloid plaques in Down's syndrome patients comprise, among other complement components, the classical pathway proteins C1q (early) and C3 (middle) (see entire document). Stoltzner teaches that "therapeutic interventions aimed at slowing or halting this cascade of inflammation in response to compacted [amyloid-beta protein] in the brain may be of value in treating or preventing AD" (page 498, last sentence in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings the teachings of Janeway regarding chimeric and/or humanized forms of antibodies with the anti-C2 monoclonal antibodies taught by Anderson because Janeway et al teaches that humanized antibodies are far less immunogenic in humans and have far less risk of anaphylaxis and because the antibody taught by Anderson et al. binds to C2a or to the C2a portion of C2, and inhibits the classical pathway. One would have been motivated to combine the teachings with a reasonable expectation of success by the teaching of Vakeva that anti-complement antibodies are effective in reducing complement-mediated damage of tissue and the teachings of Stoltzner that early complement proteins also have a damaging effect in inflammation and that it is desirous to interfere with the classical cascade at an earlier, rather than a later, stage. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (Biochem. Soc. Trans. 1987, 15(4):660-661; of record) in view of U.S. Patent No. 5,861,156 to George et al. (of record), Vakeva et al. (Circulation. [1998] 97(22):2259-2267; U on form PTO-892, newly cited) and Stoltzner et al (Am J Pathol. [2000]156(2):489-499; V on form PTO-892, newly cited).

Anderson has been discussed supra.

Anderson does not teach fragments of the antibody as recited in claim 22.

The '156 patent teaches in Column 10, lines 42-62, that the complete antigen binding site of an antibody may be obtained by recombinant methods from monoclonal antibodies or combinatorial libraries, and may correspond to the two-chain 50 kD Fab or related Fab' fragments, the two-chain 25 kD Fv fragment, or the 26-27 kD single-chain Fv. '156 teaches that all of these species are smaller and far more rapid in biodistribution than IgG monomers or dimmers and that their reduced is advantageous for primary targeting.

Vakeva teaches that "[s]everal lines of investigation support a role for complement in the pathogenesis of [myocardial infarction/reperfusion] injury" (page 2259, first column in particular). Vakeva teaches that treatment of rats with an anti-C5 antibody "significantly inhibits cell apoptosis, necrosis and [peripheral mononuclear cell] infiltration in the rat despite C3 deposition" (Abstract in particular). C5 is known in the art to be a "late" component in the complement cascade and C3 is similarly known to be an "early" or "middle" component.

Stoltzner teaches that the complement system mediates the inflammatory response activated in Alzheimer's disease (AD; Abstract in particular). Stoltzner teaches that AD amyloid plaques in Down's

syndrome patients comprise, among other complement components, the classical pathway proteins C1q (early) and C3 (middle) (see entire document). Stoltzner teaches that "therapeutic interventions aimed at slowing or halting this cascade of inflammation in response to compacted [amyloid-beta protein] in the brain may be of value in treating or preventing AD" (page 498, last sentence in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of the '156 patent regarding Fab, $F(ab)_2$, Fv or ScFv forms of antibodies with the anti-C2 monoclonal antibodies taught by Anderson because the '156 patent teaches that antibody fragments are smaller and far more rapid in biodistribution than IgG monomers or dimers and that their reduced size is advantageous for primary targeting, and because the antibody taught by Anderson binds to C2a or to the C2a portion of C2, and inhibits the classical pathway. One would have been motivated to combine the teachings with a reasonable expectation of success by the teaching of Vakeva that anti-complement antibodies are effective in reducing complement-mediated damage of tissue and the teachings of Stoltzner that early complement proteins also have a damaging effect in inflammation and that it is desirous to interfere with the classical cascade at an earlier, rather than a later, stage. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Request for Rejoinder

10. Applicant's request for rejoinder with reference to MPEP 821.04 is acknowledged. However, as the product claims have not been found to be allowable in the present Office Action, the withdrawn claims to methods of using the product are not being rejoined and stand as withdrawn.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (703) 305-4441. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in

Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Effective January 8, 2004, the Examiner's telephone number will be (571) 272-0852.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
November 26, 2003

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
12/1/03